

RESEARCH COMMUNICATION

Factors Affecting Residual Lesion in Women with Cervical Adenocarcinoma In Situ after Cone Excisional Biopsy

Jatupol Srisomboon^{1*}, Chumnann Kietpeerakool¹, Prapaporn Suprasert¹, Sumalee Siriaungkul², Surapan Khunamornpong², Wiboonwan Prompittayarat¹

Abstract

The objective of this study was undertaken to evaluate the factors affecting residual lesion in women with adenocarcinoma in situ (AIS) on cervical conization specimens. The medical records of women with AIS who had no associated invasive carcinoma after cervical conization and underwent subsequent hysterectomy at Chiang Mai University Hospital were reviewed. During March 1998 and March 2006, 45 women were included for analysis. The mean age was 45.2 years (range, 30-66 years). Thirteen (28.9%) women presented with AIS on Pap smear. Thirty (66.7%) underwent loop electrosurgical excision procedure and the remaining 15 (33.3%) underwent cold-knife conization. Twenty (44.4%) women had mixed lesions of AIS and squamous intraepithelial lesion on cervical specimens. Surgical cone margins were clear in 25 (55.6%) women. Eighteen (40%) and two (4.4%) women had involved and non-evaluable cone margins, respectively. Residual lesion was noted in 14 (31.1%) hysterectomy specimens. There was no residual lesion in women with clear cone margins while 72% and 50% of women with involved and non-evaluable cone margins, had residual lesion, respectively. These differences were statistically significant ($P < 0.001$). No significant association between the ECC results and the residual lesion was noted ($P = 0.29$). In conclusion, approximately one-third of women with AIS on cervical conization have residual lesion on subsequent hysterectomy specimens. Only cone margin status is a significant predictor for residual lesion.

Key Words: Adenocarcinoma in situ - cone margin - residual lesion - endocervical curettage

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Introduction

Adenocarcinoma in situ (AIS) of the uterine cervix is currently well established as a precancerous lesion of invasive adenocarcinoma similar to squamous cell carcinoma in situ. Compared to invasive squamous cell carcinoma, the incidence of invasive cervical adenocarcinoma is relatively increased even in the areas with effective structural program of cervical cancer screening (Vizcaino et al., 1998, Vizcaino et al., 2000, Wang et al., 2004). These findings show that the current prevention strategies may be ineffective in detecting a precursor lesion of cervical adenocarcinoma (Castellsague et al., 2006).

The diagnosis of cervical AIS may be difficult because only 50% of the patients had cytologic abnormality suggestive of glandular disease, although 85% to 100% of such patients presented with abnormal cervical cytology (Krivak et al., 2001). When the diagnosis of a glandular lesion of the cervix is suggested by cytology, endocervical curettage (ECC), colposcopy or punch biopsy, a deep excisional cone biopsy is required to confirm the diagnosis

and rule out the presence of invasive adenocarcinoma. The methods for diagnostic excision of the cervix include cold knife conization (CKC), laser cone excision, and loop electrosurgical excision procedure (LEEP). Management of cervical AIS is still controversial because of conflicting data regarding the status of cone biopsy margins and the incidence of residual lesion in the cervix (Im et al., 1995, Wolf et al., 1996, Azodi et al., 1999, Krivak et al., 2001). This study was undertaken accordingly to evaluate the treatment outcomes and factors affecting residual lesion in women with cervical AIS undergoing diagnostic cone excision and subsequent hysterectomy.

Materials and Methods

After approval of the Research Ethics Committee, the medical records of women diagnosed with AIS who had no associated invasive carcinoma after cervical conization and underwent subsequent hysterectomy at Chiang Mai University Hospital between March 1998 and March 2006 were reviewed. All enrolled women had their histological materials initially reported or reviewed by

¹ Department of Obstetrics and Gynecology, ² Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand *For Correspondence: E-mail: jsrisomb@mail.med.cmu.ac.th

the gynecological pathologists at our institute at the time of treatment. The women who had mixed lesions of AIS and squamous intraepithelial lesion (SIL) of any grade were also recruited. The baseline characteristics, cone histology, cone margin status, results of ECC, and residual lesion after cervical conization were analyzed.

The conization specimens from either loop electrosurgical excision procedure (LEEP) or cold knife conization (CKC) were sectioned in their entirety. All specimens were opened longitudinally and sectioned serially along the entire length from the endocervix to the ectocervix at interval of 1-3 mm and then embedded in paraffin. The surgical margins of the cones were marked with indelible ink. Sections were stained with hematoxylin and eosin. Cone margin status was classified into three categories: (1) negative cone margins, (2) positive cone margins, (3) non-evaluable cone margins. Negative cone margin was defined as the absence of neoplastic epithelium of any grade at all cone margins by pathological examination. Positive margin was defined as the presence of neoplastic epithelium of any grade at any cone margin. Non-evaluable margin was defined as at least one margin unable to determine for the margin status while the other margins were negative. The residual cervix in the hysterectomy specimens was sectioned like a cone for histological examination.

The ECC specimens were histologically interpreted as negative, positive, or inadequate. The results were negative when normal endocervical cells were presented. Positive results were those in which neoplastic cells were noted. Inadequate results were those without cells for interpretation.

Statistical analysis was performed using Mann-Whitney U test, student' t test, chi-square test, and Fisher exact test when appropriate. A P-value of less than 0.05 was considered statistical significance. All tests were two sided and conducted with SPSS computer software (SPSS Inc, Chicago, Ill).

Results

During the study period, 1,957 women underwent cervical conization at Chiang Mai University Hospital and 51 women who had AIS without any associated invasive lesion on conization specimens were identified which accounted for 2.6% (95% confidence interval [CI] = 1.9 to 3.4). Six women were excluded because of loss to follow-up (3), and declination for subsequent hysterectomy (3), allowing 45 women for further analysis. Surgicopathological characteristics of the 45 women are presented in Table 1. The mean age at diagnosis was 45.2 years (range: 30-66 years). The majority of women (71.1%) were premenopausal. Two (4.4%) women were nulliparous. The most common contraception was oral combined pill (28.9%), followed by tubal resection (22.2%), and depot medroxyprogesterone acetate (13.3%). One woman (2.2%) had positive screening for HIV infection. Twenty (44.4%) women presented with Pap smear suggesting glandular abnormality. The colposcopically-directed biopsy before conization revealed AIS in only 11 (24.4%) women. Thirty (66.7%)

conization procedures were LEEP and the remaining 15 (33.3%) were CKC. The average maximum cone base diameter of LEEP and CKC specimens were 22.3 mm and 32.5 mm, respectively. The average cone length of LEEP and CKC specimens were 9.3 mm and 15.6 mm, respectively. The differences of either cone base or cone length between these two conization techniques were statistically significant (P<0.001). The conization specimens demonstrated AIS alone in 25 women. The remaining 20 women had coexisting squamous cell lesion, i.e. high-grade squamous intraepithelial lesion (HSIL). The overall incidence of cone margin involvement was 40%. When stratified by the method of cervical conization, such incidence was noted in 46.7% and 26.7% of specimens from LEEP and CKC, respectively. The cone margin status could not be evaluated in 2 LEEP specimens due to severe thermal artifact. The histology of involved lesion was AIS in 10 (22.2%) women, AIS with HSIL in 2 (4.4%), atypical endocervical epithelium and HSIL in 3 (6.7%). The median time interval from cervical conization to subsequent hysterectomy was 8 weeks with a range of 3-16 weeks. Residual lesion was noted in 14 subsequent hysterectomy specimens (31.1%, 95% CI= 18.2% to 46.6%). There was no residual lesion in women whose cone margins were free while 72% and 50% of women with involved and non-evaluable cone margins had residual lesion, respectively. Of 10 women who had AIS involving the cone margins, 6 had residual AIS on hysterectomy specimens, the remaining 4 had no residual lesion. Of 3 women with atypical endocervical epithelium at the cone margins, 2 had residual AIS while the remaining one had HSIL on subsequent hysterectomy specimen. Among 2 women who had AIS and HSIL involving cone margins,

Table 1. Surgico-Pathological Characteristics of the 45 Women with AIS Histology.

| Characteristics | Number (%) |
|-----------------------------|------------|
| Preceding cervical cytology | |
| HSIL | 14 (31.1) |
| AIS | 13 (28.9) |
| AGC | 6 (13.3) |
| SCCA | 5 (11.1) |
| ASC | 3 (6.7) |
| Adenocarcinoma | 1 (2.2) |
| Unknown | 3 (6.7) |
| Cone margin involvement | |
| Negative | 25 (55.6) |
| Positive | 18 (40.0) |
| Non-evaluable | 2 (4.4) |
| Endocervical curettage | |
| Not done | 13 (28.9) |
| Normal | 21 (46.7) |
| Abnormal | 15 (11.1) |
| Inadequate | 6 (13.3) |
| Residual lesion | |
| Absence | 31 (68.9) |
| AIS | 10 (22.2) |
| AIS with HSIL | 1 (2.2) |
| HSIL | 3 (6.7) |

Abbreviations: HSIL, high grade squamous intraepithelial lesion; AIS, adenocarcinoma in situ; AGC, atypical glandular cells; SCCA, squamous cell carcinoma; ASC, atypical squamous cells.

one had residual AIS, the remaining one had residual AIS and HSIL. Of 3 women with HSIL involving the cone margins, 2 had residual HSIL, the remaining one had no residual lesion. In 2 cases of non-evaluable cone margin status, the hysterectomy specimens revealed residual AIS (1) and no residual lesion (1).

Table 2. displays the association between the residual lesion on subsequent hysterectomy specimens versus cone margin involvement and ECC results. The cone margin status was noted to be a significant predictor for residual lesion ($P < 0.001$). No significant association between ECC results and residual lesion was observed ($P = 0.29$).

Discussion

AIS of the uterine cervix is an uncommon cervical precancerous lesion. In our 9-year experience, the histological diagnosis of such lesion accounted for only 2.6% of all cervical conization specimens. Because of its rarity, the number of reported cases in the literature remains low.

The sensitivity of either cervical cytology or colposcopy in predicting AIS is suboptimal. In the literature, AIS cases were detected only 10% to 30% by Pap smear and 30% to 50% by colposcopically directed biopsy (CDB) before cervical conization (Muntz et al., 1992, Wolf et al., 1996, Azodi et al., 1999, Ostor et al., 2000, Kennedy and Biscotti, 2002). In the present study, 28.9% and 24.4% of women with AIS histology were detected by Pap smear and CDB before cervical conization, respectively. Because of the poor predictive value of either Pap smear or colposcopy, cervical conization remains the gold standard for establishing the histological diagnosis of AIS.

In this study, the incidence of coexisting squamous intraepithelial lesion (SIL) was 44.4%, which was in accordance with the previous reports ranging from 28% to 64% (Wolf et al., 1996, Denehy et al., 1997, Azodi et al., 1999). The presence of coexisting SIL may be related to the low sensitivity of cervical cytology. In addition SIL may obscure the abnormality of glandular component.

Cone margin status is a significant predictor for residual disease of women with AIS of the cervix. If the cone margins are involved, it is generally accepted that subsequent hysterectomy is indicated because of the high incidence of persistent disease in the residual cervix ranging from 50 to 70% (Anderson and Arffmann, 1989, Muntz et al., 1992, Im et al., 1995, Wolf et al., 1996, Denehy et al., 1997, Ostor et al., 2000, Shin et al., 2000). In the present study, the residual lesion rate of 72% in women with positive cone margins is comparable to the aforementioned series. Subsequent management in women who have negative cone margins for AIS is still inconclusive. The reported incidence of residual disease on subsequent hysterectomy in AIS cases with negative cone margins are inconsistent ranging from 0 to 44% (Anderson and Arffmann, 1989, Muntz et al., 1992, Im et al., 1995, Wolf et al., 1996, Denehy et al., 1997, Ostor et al., 2000, Shin et al., 2000). In our study, there was no residual lesion on subsequent hysterectomy specimens in women with clear cone margins. The discrepancy of this

Table 2. Predictors for Residual Lesions on Subsequent Hysterectomy Specimens

| Variables | Category | Residual (%) | P-value |
|-----------------------------|---------------|--------------|---------|
| Margin involvement (N = 45) | Negative | 0/25 (0.0) | < 0.001 |
| | Non-evaluable | 1/2 (50.0) | |
| | Positive | | |
| | Endocervical | 17/10 (70.0) | |
| | Ectocervical | 4/5 (80.0) | |
| | Both margins | 2/3 (66.7) | |
| ECC (N = 32) | Abnormal | 3/5 (60.0) | 0.29 |
| | Normal | 4/21 (19.0) | |
| | Inadequate | 2/6 (33.3) | |

ECC, endocervical curettage

result may be partly explained by the difference in the specimen processing, type of conization method, and the experience in histological diagnosis of AIS. However, based on our findings, woman who wishes to preserve fertility may be conservatively managed with cervical conization alone if the clear cone margins are obtained. Nevertheless, the data on residual lesion reported in the literature should be informed to the women during treatment planning.

ECC after cervical conization, theoretically appears to be a predictor of the residual lesion in women with AIS. However, these results in the literature are mixed. Lea et al (2002) reported that only 5.9% of women with negative ECC had residual lesion. Conversely, Denehy et al (1997) and Azodi et al (1999) noted that approximately 60% of such women had residual lesion on subsequent surgical excision. In our study, although ECC was not consistently performed in all cases, approximately 20% of women with negative ECC had residual lesion on subsequent hysterectomy specimens. Our finding supports that negative ECC in women with AIS of the cervix does not assure the absence of lesion on the residual cervix.

The results from the present study also suggested that CKC should be the preferred conization method for diagnosis and management of AIS because it provides a greater depth and larger volume of cone specimens, resulting in the lower incidence of positive cone margins than those by LEEP. Additionally, the cone margin status of CKC specimens can be determined more accurately than those by LEEP specimens whose margins sometimes cannot be evaluated due to coagulation artifact.

The limitations of this study are the retrospective by nature, the small number of patients with AIS of the uterine cervix, and the bias of attending physicians performing diagnostic cervical excision. The strengths of this study include the single institution experience and the evaluation methods of the residual lesion on the hysterectomy specimens not on the repeat cone specimens.

In conclusion, approximately one-third of women with AIS on cervical conization have residual lesion based on subsequent hysterectomy specimens. Cone margin status is a significant predictor for residual lesion. Women with AIS who strongly desire to preserve future fertility could be conservatively treated by cervical conization provided the cone margins are clear. If cone margins are involved, re-excision is recommended in women who wish to maintain reproductive potential.

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